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Insulin resistance predicts rapid virological response in non-diabetic, non-cirrhotic genotype 1 HCV patients treated with peginterferon alpha-2b plus ribavirin: Some issues

To the Editor:

We read with great interest the report by Grasso et al. in a recent issue of the *Journal of Hepatology* [1]. They enrolled 90 consecutive, non-diabetic, non-cirrhotic patients with genotype 1 chronic hepatitis C, treated with peginterferon alpha-2b plus ribavirin. Two issues need clarification.

The first concerns the unit of sensitivity of the qualitative reverse-transcription PCR test, Roche Cobas Amplicor assay which was mistakenly written as copies per millilitre in this paper. It should be international units per millilitre [2].

Secondly, rapid virological response (RVR) [3,4] and homeostasis model assessment of insulin resistance (HOMA-IR) [5,6] have been important factors associated with achievement of a sustained virological response (SVR). However, the current study observed that HOMA-IR could predict rapid virological response (RVR) but not SVR [1]. There is low probability of normal distribution for HOMA-IR. For example, the mean value and standard deviation of HOMA-IR was 2.6 and 2.1, respectively, in the current study. Therefore, non-parametric inferential statistical methods or logarithmic transformation of original values to improve skewness before analyses are preferred in this situation.

References

[1] Grasso A, Malfatti F, Leo PD, Martines H, Fabris P, Toscanini F, et al. Insulin resistance predicts rapid virological response in non-diabetic, non-cirrhotic genotype 1 HCV patients treated with peginterferon alpha-2b plus ribavirin. J Hepatol 2009;23:23.

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Insulin resistance predicts rapid virological response in non-diabetic, non-cirrhotic genotype 1 HCV patients treated with peginterferon alpha-2b plus ribavirin: A clarification

To the Editor:

We read with interest the comment by Wu and colleagues on our recently published paper [1]. Two issues indeed need to be clarified.

The unit of sensitivity of the qualitative reverse-transcription PCR test, Roche Cobas Amplicor assay, was mistakenly reported in the Patients and methods section as copies per millilitre, rather than as international units per millilitre. We apologize for this oversight.

Regarding the second issue, although equal variance was found between the two groups (SVR and no-SVR), when the Levene test was applied to HOMA-IR, a Kolmogorov–Smirnov test confirmed a non-normal distribution of HOMA-IR values, as suggested by Wu and colleagues. The Mann–Whitney test, which had actually been applied in our former analysis, failed to demonstrate a significant difference in HOMA-IR between patients with and without SVR, although the *p*-value was slightly better than the one reported in Table 1. Nevertheless, we agree that this clarification should have been included in the statistical analysis section.

Reference

[1] Grasso A, Malfatti F, De Leo P, Martines H, Fabris P, Toscanini F, et al. Insulin resistance predicts rapid virological response in non-diabetic, non-cirrhotic genotype 1 HCV patients treated with peginterferon alpha-2b plus ribavirin. J Hepatol 2009;23:23.

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Insulin resistance and HCV virologic response to peg-interferons (Peg-IFN) with ribavirin (RBV) in HIV/HCV co-infected patients

To the Editor:

In the recently published article by Merchante et al. [1] insulin resistance, analyzed as HOMA value [(fasting insulin mU/ml × fasting glucose mmol/l)/22.5)], was not associated with sustained virologic response (SVR) to anti-HCV combination therapy in HIV/HCV co-infected patients. In that retrospective cohort study, 36% of 155 patients achieved SVR. At multivariate analysis, HCV genotype 3, lower baseline HCV-RNA and higher baseline LDL-cholesterol were independently correlated to SVR. On the contrary, the HOMA index, considering a cut-off of 4, did not show any correlation with SVR, even after excluding cirrhotic patients from the analysis.

In our clinic, we retrospectively analyzed 86 HIV/HCV co-infected patients treated with Peg-IFN with RBV. At HCV treatment initiation their median age was 42 years, 67% were males, 77% injecting drug users, 88% on combination anti-retroviral treatment (cART), their median CD4 was 478 cells/mm^3; 85% had HCV-RNA >400,000 IU/ml, 33% with HCV genotype 3, 64% HCV genotype 1 or 4; 30% showed a Metavir fibrosis score of F3–F4. Patients were treated with Peg-IFN + RBV (80% Peg-IFN α2a) for a median of 43.1 weeks (41% of patients reaching 48 weeks of treatment). Fasting IR was determined at baseline, 12 and 48 weeks of HCV therapy. IR was calculated using the HOMA index (IR ⩾ 2.6), Quicki index (IR ⩽0.33) and McAuley index (IR ⩽5.8) and the different values were correlated with early virologic response (12 weeks, EVR), end of treatment response (ETR) and sustained virological response (SVR) by logistic regression analysis. EVR was achieved in 67.4%, ETR in 66.2%, SVR in 37.2%. IR at baseline 12 and 48 weeks was 2.0 (Q1–Q3 1.4–3.3), 2.1 (1.4–3.3) and 2.1 (1.3–4.1), according to HOMA index; 0.34 (0.32–0.36), 0.34 (0.32–0.36) and 0.34 (0.31–0.37) according to Quicki index and 6.4 (5.3–7.3), 5.9 (4.6–7.1) and 6.0 (4.7–7.5), according to McAuley index, respectively. No significant longitudinal changes of the IR indexes were observed. HCV genotype 3 was weakly associated with a lower baseline McAuley index (mean difference −0.77 $p = 0.06$). Genotype 3 was the only variable significantly associated with any type of response: EVR (OR vs genotype 1 or 4: 6.6, 95%CI 2.1–21), ETR (8.38;2.66–26.41) and SVR (6.96;2.81–17.23). Moreover, baseline HCV-RNA <400,000 IU/ml also significantly predicted SVR (OR 0.22; 0.07–0.70). Concerning IR measures, only baseline or week 12 Quicki index ⩽0.33 showed a slight correlation with reduced probability of ETR ($p = 0.048$), while no other IR index showed an association with any other end-point, even in the analysis stratified by viral genotype (see Table 1).

Our data showed similar results compared with those of Merchante et al. The two case series are quite similar for baseline characteristics, as well as for outcomes of anti-HCV treatment (36% vs 37.2% of SVR), suggesting the absence of relevant biases. In both studies IR was not correlated with anti-HCV treatment response, considering not only SVR, as Merchante et al. did, but also EVR and ETR as we did. Moreover, we tried to explore IR indexes other than HOMA (Quicki and McAuley) failing to find any relevant correlation with treatment outcome except for a slight association between Quicki index and ETR. In agreement with the study of Merchante et al. our study confirms the lack of a relevant role of IR in predicting SVR in HIV/HCV co-infected patients. Moreover, our data indicate that IR does not predict virological response to anti-HCV treatment in any HCV genotype group.

In contrast to these studies, Nasta and coworkers [2] identified a significant association between IR and rapid virological response (RVR, achievement of undetectable HCV-RNA at week 4: 27% of probability in patients with IR vs 54% in those without). They did not evaluate either ETR or SVR, so that we cannot speculate about the consistency of the results with a more stringent

Table 1. Crude associations of different insulin resistance indexes with virological outcomes of HCV therapy in all HCV/HIV co-infected patients and divided by HCV genotypes (univariate logistic regression).

	All patients			Genotype 3			Genotype 1, 4		
	EVR	ETR	SVR	EVR	ETR	SVR	EVR	ETR	SVR
HOMA ⩾2.6	0.69 (0.22–2.14)	0.60 (0.21–1.76)	1.29 (0.45–3.72)	0.77 (0.06–10.49)	0.18 (0.01–2.42)	0.67 (0.11–4.21)	0.71 (0.19–2.61)	0.83 (0.24–2.89)	2.30 (0.54–9.76)
Quicki ⩽0.33	0.47 (0.15–1.42)	0.34 (0.12–0.99)	0.69 (0.25–1.94)	1.27 (0.10–16.81)	0.29 (0.02–3.83)	0.24 (0.04–1.51)	0.37 (0.10–1.35)	0.34 (0.10–1.17)	1.36 (0.33–5.61)
Mc Auley ⩽5.8	0.60 (0.20–1.84)	0.55 (0.19–1.58)	1.38 (0.49–3.88)	0.57 (0.04–8.05)	0.13 (0.01–1.87)	1.20 (0.17–8.66)	0.74 (0.21–2.62)	0.92 (0.27–3.08)	2.62 (0.62–11.19)

Values represent odds ratios (95% confidence intervals). EVR, early virological response; ETR, end of treatment response; SVR, sustained virological response.